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Autonomic Dysfunctions in Parkinsonian Disorders

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Background and Purpose: Symptoms of autonomic dysfunctions are common in the patients with parkinsonian disorders. Because clinical features of autonomic dysfunctions are diverse, the comprehensive evaluation is essential for the appropriate management. For the appreciation of autonomic dysfunctions and the identification of differences, patients with degenerative parkinsonisms are evaluated using structured questionnaire for autonomic dysfunction (ADQ). **Methods:** Total 259 patients, including 192 patients with [idiopathic Parkinson's disease (IPD, age 64.6 ± 9.6 years)], 37 with [multiple system atrophy (MSA, 62.8 ± 9.1)], 9 with [dementia with Lewy body (DLB, 73.9 ± 4.3)], and 21 with [progressive supranuclear palsy (PSP, 69.4 ± 9.6)]. The ADQ was structured for evaluation of the presence of symptoms and its severity due to autonomic dysfunction, covering gastrointestinal, urinary, sexual, cardiovascular and thermoregulatory domains. Patients were also evaluated for the orthostatic hypotension. **Results:** Although dementia with Lewy body (DLB) patients were oldest and duration of disease was longest in IPD, total ADQ scores of MSA and PSP (23.9 ± 12.6 and 21.1 ± 7.8) were significantly increased than that of IPD (15.1 ± 10.6). Urinary and cardiovascular symptom scores of MSA and gastrointestinal symptom score of PSP were significantly worse than those of IPD. The ratio of patient with orthostatic hypotension in IPD was 31.2% and not differed between groups (35.1% in MSA, 33.3% in DLB and 33.3% in PSP). But the systolic blood pressure dropped drastically after standing in patients with MSA and DLB than in patients with IPD and PSP. **Conclusions:** Patients with degenerative parkinsonism showed widespread symptoms of autonomic dysfunctions. The severity of those symptoms in patients with PSP were comparing to that of MSA patients and worse than that of IPD. **Journal of Movement Disorders 2009;2:72-77**

Key Words: Parkinsonism, Autonomic dysfunction, Orthostatic hypotension.

Introduction

Autonomic dysfunction is common in Lewy body disorders, such as idiopathic Parkinson's disease (IPD), multiple system atrophy (MSA), dementia with Lewy body (DLB).[1] Symptoms of autonomic dysfunction are variable, including cardiovascular, gastrointestinal, urogenital and sudomotor symptoms and also sleep and respiratory disorders.[2]

Although autonomic dysfunction is closely associated with MSA, but nearly all parkinsonian patients experience some degree of autonomic disturbances during the course of their illness.[3] Dysautonomic symptom influences safety and quality of life, and it also burdens not only to patients but also to caregivers. And recurrent autonomic symptoms such as constipation or orthostatic dizziness can be a major cause of morbidity in these disorders. Previous studies had indicated high prevalence of autonomic symptoms in parkinsonian disorders.[4] However, few study had attempted comprehensive assessment of widespread aspects of autonomic dysfunction by conducting systemic interview evaluating autonomic symptoms in parkinsonian disorders.

The aim of this study was to examine the prevalence and frequency of dysautonomic symptoms and its differences among various parkinsonian disorders.

Material and Methods

We studied 259 consecutive patients with degenerative parkinsonisms [(IPD, MSA, DLB

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and progressive supranuclear palsy (PSP)] who visited our Parkinson & Movement disorder center and gave consent the study. The diagnosis of IPD was established according to the criteria of the United Kingdom Brain Bank and MSA, DLB and PSP diagnosed according to consensus criteria each disorder.[5-9]

All patients were evaluated for the presence of orthostatic hypotension regardless of symptoms of orthostatic dizziness or syncope. Orthostatic hypotension was measured with monitoring systolic and diastolic blood pressure and heart rate. After 10 minutes period of lying down, systolic and diastolic blood pressures were checked in the 1, 3 and 5 minutes after stand up. If the patient can't stand up by self, tilt table was used. Orthostatic hypotension was defined as a drop in systolic blood pressur (BP) >20 mmHg or diastolic BP >10 mmHg anytime during stand up.

Comprehensive assessment of autonomic dysfunction was assessed using systematized autonomic dysfunction questionnaire (ADQ).[10] ADQ covered gastrointestinal symptoms, urinary symptoms, sexual dysfunction, cardiovascular symptoms and thermoregulary symptoms. Gastrointestinal symptoms included salivation, dysphagia, nausea, constipation and defecatory dysfunction (anismus). Urinary symptoms included hesitancy, urgency, incomplete voiding, weak stream, frequency, nocturia and urinary incontinence. Sexual symptoms included erectile dysfunction in achievement and maintenance, change of libido. Cardiovascular symptoms included orthostatic hypotension and syncope. Thermoregulatory symptoms included sweating problem in face, trunk and limbs and heat intolerance, cold intolerance, oiliness and seborrhea (Table 1). In order to estimate severity of each symptom, subjects were asked to rate frequency or severity of symptoms over a period of the preceding 7 days or 10 episodes. The severity of symptoms was graded from 0 to 4 (0; normal, 1; mild, 2; moderate, 3; severe dysfunction, 4; maximum possible abnormality), so the total score ranged from 0 to 96.

Characteristic of each disorders were evaluated as duration of symptoms and treatment, Hoehn and Yahr (HY) stage and modified Schwab and England activities of daily living (SEADL). All co-morbid medical conditions, which could cause or affect autonomic symptoms, were recorded.

All patients gave the written informed consent, and this study approved by institutional review board. Statistical Package for Social Sciences (SPSS) version 14 (SPSS Inc, Chicago, IL, USA) for Windows was used for statistical calculations. Chi-square test was used for categorical variables and analysis of variance between groups (ANOVA) with Dunnett's T3 as posthoc tests was used for continuous variables. Statistical significance was declared at $p<0.05$ level.

Result

Among the total 259 patients, 192 patients were IPD (72 males), 37 MSA (16 males), 21 PSP (11 males) and 9 DLB (5 males). The male to female ratio was low in IPD and MSA, but there was no significant difference between groups. The DLB patients were oldest and mean age of PSP and DLB were higher than those of IPD and MSA. Duration of symptoms and treatment was longest in IPD patients but HY stage

Table 1. Autonomic dysfunction questionnaire (ADQ)

Gastrointestinal symptoms	Urinary symptoms	Sexual dysfunction	Cardiovascular symptoms	Thermoregulatory symptoms
Salivation	Hesitancy	Erectile dysfunction	Orthostasis	Sweating (Face)
Dysphagia	Urgency	Ejaculation difficulty	Syncope	Sweating (Trunk)
Nausea	Incomplete voiding	Libido change		Sweating (Limb)
Constipation	Weak stream			Heat intolerance
Defecatory dysfunction (anismus)	Frequency			Cold intolerance
	Nocturia			Oiliness & seborrhea
	Urinary incontinence			

Table 2. General characteristics of patients

Group (number)	IPD (192)	MSA (37)	PSP (21)	DLB (9)	Total (259)	*p*
Sex (M : F)	72 : 120	16 : 21	11 : 10	5 : 4	108 : 156	ns
Age (year)	64.6 ± 9.6	62.8 ± 9.1	69.4 ± 6.9	73.8 ± 4.3	65.1 ± 9.4	PSP, DLB > IPD, MSA
K-MMSE	25.0 ± 3.8	25.3 ± 3.4	23.7 ± 5.2	18.4 ± 5.7	24.7 ± 4.1	ns
Duration of symptoms (y)	5.1 ± 4.9	2.2 ± 1.4	3.5 ± 2.1	2.3 ± 2.2	4.5 ± 4.4	IPD > MSA, PSP, DLB
Duration of treatment (y)	3.0 ± 4.3	0.5 ± 1.0	1.1 ± 1.7	1.1 ± 1.8	2.4 ± 3.9	IPD > MSA, PSP
Hoehn & Yahr stage	2.5 ± 0.7	2.9 ± 0.8	3.3 ± 0.9	3.3 ± 0.9	2.7 ± 0.8	PSP > IPD
SEADL	69.7 ± 15.5	60.6 ± 23.1	55.0 ± 27.8	45.0 ± 12.9	66.7 ± 18.4	ns

IPD: idiopathic Parkinson's disease, MSA: multiple system atrophy, PSP: progressive supranuclear palsy, DLB: dementia with Lewy body, K-MMSE: Korean version of mini-mental status exam, SEADL: Schwab and England activity of daily living.

was significantly higher in the patients with PSP than IPD. SEADL and score of mini-mental status examination were low in DLB patient but did not reach statistical significance. There was no problem to take the history of dysautonomic symptoms due to cognitive dysfunction (Table 2).

The prevalence of orthostatic hypotension was similar among the groups (IPD; 31.2%, MSA; 35.1%, PSP; 33.3% and DLB; 33.3%). The drop of blood pressure after stand up was most prominent in DLB patient but significant difference was only found between MSA and IPD patients in systolic pressure (Table 3).

In the results of interview with ADQ, the distribution of most frequent symptoms was different between the disorders. Although urinary symptoms were the most frequent symptoms in all disorders, nearly all patients (over 94% of patients) complained in MSA and PSP but three quarters in IPD and DLB. Nocturia was most common in urinary symptoms, followed by frequency, urgency and weak stream. In gastrointestinal domain, the most frequent symptom was constipation, which followed by salivation and anismus, but patients with PSP most commonly complained dysphagia. In general, the order of frequent symptom were following; nocturia (79.2%), frequency of urination (62.1%), constipation (47.1%), urgency of urination (44.6%), weak stream of urination (44.2%), change of libido (41.3%), incomplete voiding after urination (40.8%), salivation (40.0%), hesitancy of urination (39.6%), anismus (38.3%), dysphagia (35.8%), orthostasis (35.4%)(Table 4).

The severity of gastrointestinal symptoms, especially dysphagia, was significant in PSP patients than other patients. The total score of gastrointestinal symptoms of PSP was higher than that of IPD and even than MSA. The nearly all urinary symptoms were most severe in MSA patients, and the severity of urgency of PSP patients were comparing to that of MSA patients. In other domains, symptoms of MSA patients were most severe than those of IPD and DLB patients, too. The total score of ADQ was highest in patients with MSA and that of PSP was comparing to MSA patients' and significantly increased than that of patients with IPD (Table 5).

The patients with orthostatic hypotension showed no difference in ADQ with the patients without orthostatic hypotension and there was no correlation with complaint of orthostasis and presence of orthostatic hypotension in IPD and PSP group. But in MSA group, the patients with orthostatic hypotension more commonly and/or severely complained cardiovascular and urinary symptoms, and the total ADQ score was higher than that of patients without (data not shown).

There was no difference in the prevalence of comorbid disease affecting autonomic symptoms between the disease group (such as hypertension, diabetes, nephropathy, benign prostatic hypertrophy), and the result in the patients without any other disorders were comparable to those of all patients (data not shown).

Discussion

Autonomic dysfunction is common clinical symptoms in neurodegenerative disorders including Lewy body disease and taupathy.[1,11] Especially, in the disorders involving dysre-

Table 3. Orthostatic hypotension in each disease group

Group (number)	IPD (192)	MSA (37)	PSP (21)	DLB (9)	Total (259)	*p*
Orthostatic hypotension	60 (31.2%)	13 (35.1%)	7 (33.3%)	3 (33.3%)	83 (32.0%)	ns
Basal systolic blood pressure	129.9 ± 19.4	127.0 ± 17.7	137.8 ± 22.1	125.9 ± 22.2	130.0 ± 19.6	ns
Basal diastolic blood pressure	79.6 ± 11.6	78.4 ± 11.6	87.4 ± 13.3	76.1 ± 7.3	80.0 ± 11.9	PSP > IPD
Mean systolic pressure drop	8.2 ± 14.1	13.8 ± 19.3	6.0 ± 11.7	22.9 ± 13.7	9.5 ± 15.1	MSA > IPD
Mean diastolic pressure drop	1.8 ± 8.7	3.8 ± 9.6	4.0 ± 13.3	5.5 ± 8.0	2.5 ± 9.4	ns

IPD: idiopathic Parkinson's disease, MSA: multiple system atrophy, PSP: progressive supranuclear palsy, DLB: dementia with Lewy body.

Table 4. Most frequent dysautonomic symptoms in each disorder

	IPD	MSA	PSP	DLB
Gastrointestinal symptom	Constipation	Constipation	Dysphagia	Constipation
	-42.60%	-55.60%	-68.40%	-47.10%
Urinary symptom	Nocturia	Nocturia	Nocturia	Nocturia
	-74.40%	-94.40%	-94.70%	-77.80%
Sexual dysfunction	Change of libido	Change of libido	Change of libido	Change of libido
	-39.20%	-50.00%	-52.60%	-22.20%
Cardiovascular symptom	Orthostasis	Orthostasis	Orthostasis	Orthostasis
	-30.70%	-52.80%	-42.10%	-44.40%
Thermoregulatory symptom	Sweat-trunk	Sweat-face	Heat intolerance	Heat intolerance
	-17.00%	-30.60%	-21.10%	-33.30%

IPD: idiopathic Parkinson's disease, MSA: multiple system atrophy, PSP: progressive supranuclear palsy, DLB: dementia with Lewy body.

Table 5. Severity of dysautonomic symptoms in each disorder

	IPD	MSA	PSP	DLB	Total	*p*
Gastrointestinal symptom						
Salivation	0.5 ± 0.7	0.6 ± 0.7	0.8 ± 0.8	1.0 ± 1.1	0.6 ± 0.7	ns
Dysphagia	0.7 ± 1.2	0.6 ± 1.1	1.6 ± 1.6	0.4 ± 1.3	0.7 ± 1.2	PSP > IPD, MSA, DLB
Nausea	0.2 ± 0.6	0.2 ± 1.6	0.2 ± 0.5	0.1 ± 0.3	0.2 ± 0.6	ns
Constipation	0.8 ± 1.1	1.1 ± 1.2	1.1 ± 1.1	1.2 ± 1.1	0.8 ± 1.1	ns
Anismus	0.8 ± 1.2	0.9 ± 1.4	1.4 ± 1.3	1.1 ± 1.2	0.9 ± 1.3	ns
Sum	3.3 ± 3.5	3.9 ± 3.2	6.3 ± 3.2	4.2 ± 2.5	3.6 ± 3.5	PSP > IPD, MSA
Urinary symptom						
Hesitancy	0.8 ± 1.3	1.8 ± 1.6	1.1 ± 1.4	1.7 ± 1.7	1.0 ± 1.4	MSA > IPD
Urgency	0.9 ± 1.3	1.5 ± 1.4	1.7 ± 1.5	0.9 ± 1.2	0.1 ± 1.3	MSA, PSP > IPD
Incomplete voiding	1.0 ± 1.4	1.7 ± 1.8	0.6 ± 1.1	1.4 ± 1.7	1.1 ± 1.5	MSA > IPD, PSP
Weak stream	1.2 ± 1.5	1.7 ± 1.7	1.0 ± 1.5	1.4 ± 1.8	1.3 ± 1.6	ns
Frequency	1.2 ± 1.3	2.1 ± 1.5	1.7 ± 1.5	0.7 ± 1.3	1.4 ± 1.4	MSA > IPD, DLB
Nocturia	1.8 ± 1.4	2.6 ± 1.1	2.2 ± 1.1	2.1 ± 1.5	2.0 ± 1.4	MSA > IPD
Incontinence	0.3 ± 0.7	0.9 ± 1.4	0.8 ± 1.3	0.3 ± 0.7	0.4 ± 0.9	MSA > IPD
Sum	7.1 ± 5.9	12.1 ± 7.0	8.6 ± 5.6	8.7 ± 6.7	8.8 ± 0.3	MSA > IPD, PSP
Sexual dysfunction						
Erectile dysfunction	0.4 ± 1.1	0.9 ± 1.6	0.5 ± 1.3	0.1 ± 0.3	0.5 ± 1.2	MSA >DLB
Ejaculation difficulty	0.4 ± 1.0	0.8 ± 1.5	0.5 ± 1.3	0.1 ± 0.3	0.4 ± 1.1	Ns
Change of libido	1.3 ± 1.8	1.7 ± 1.8	1.9 ± 2.0	0.6 ± 1.3	1.4 ± 1.8	PSP > DLB
Sum	2.1 ± 3.1	3.4 ± 4.1	2.9 ± 3.8	0.8 ± 1.6	2.3 ± 3.3	MSA, PSP > DLB
Cardiovascular symptom						
Orthostasis	0.7 ± 1.3	1.7 ± 1.8	1.3 ± 1.6	1.3 ± 1.8	0.8 ± 1.4	MSA > IPD
Syncope	0.1 ± 0.3	0.1 ± 0.4	0	0	0.1 ± 0.3	ns
Sum	0.8 ± 1.4	1.8 ± 1.9	1.2 ± 1.6	1.3 ± 1.8	1.0 ± 1.5	MSA > IPD
Thermoregulatory symptom						
Sweat-face	0.4 ± 1.0	0.8 ± 1.4	0.3 ± 0.7	0.2 ± 0.4	0.4 ± 1.0	MSA > DLB
Sweat-trunk	0.4 ± 1.0	0.6 ± 1.3	0.3 ± 0.1	0.2 ± 0.4	0.3 ± 0.8	ns
Sweat-limb	0.3 ± 0.8	0.3 ± 0.8	0.4 ± 0.8	0.2 ± 0.4	0.3 ± 0.8	ns
Heat intolerance	0.3 ± 0.8	0.5 ± 1.2	0.4 ± 1.0	0.4 ± 0.7	0.3 ± 0.9	ns
Cold intolerance	0.3 ± 0.8	0.3 ± 0.7	0.3 ± 0.9	0.4 ± 0.9	0.3 ± 0.8	ns
Oiliness, seborrhea	0.1 ± 0.5	0.3 ± 0.6	0.3 ± 0.9	0.2 ± 0.7	0.2 ± 0.6	ns
Sum	1.6 ± 3.6	2.8 ± 4.1	2.1 ± 4.8	1.8 ± 2.9	1.9 ± 3.7	ns
Total score	15.1 ± 10.6	23.9 ± 12.6	21.1 ± 7.8	16.8 ± 7.2	17.0 ± 11.1	MSA, PSP > IPD

IPD: idiopathic Parkinson's disease, MSA: multiple system atrophy, PSP: progressive supranuclear palsy, DLB: dementia with Lewy body.

gulation of alpha-synuclein, symptoms result from degeneration in autonomic regulatory regions of the brain or peripheral autonomic ganglia.[12] The presence and distribution of Lewy bodies has led to a clinicopathological classification of Lewy body disorder spectrum, where brainstem localization correlates with motor parkinsonism, diffuse cortical localization with dementia, and brainstem, spinal cord, and sympathetic ganglia localization with autonomic dysfunction.[2,13] In the patients with IPD, dysautonomic symptoms were more prevalent than those of control subjects, and the presence of orthostatic hypotension was up to 58.2% in early stage of disease.[2,14,15] It is generally believed that autonomic symptoms develop earlier and more severe in MSA than IPD and other atypical syndromes, but some reports showed high prevalence in other disorders.[16,17]

Dysautonomic symptoms negatively impact on patient's safety and quality of life. Orthostatic hypotension can severely limit daily activities of patients, and nocturia and urinary frequency frequently cause the sleep disturbance. Although the dysautonomia might not correlate with other parkinsonian symptoms or sign, if the autonomic dysfunction in these degenerative disorders could respect the widespread involvement of pathology, the patient with severe autonomic dysfunction would have more extensive non-motor symptoms

and poor prognosis. There were several evidences of the correlation between dysautonomic symptoms and cognitive dysfunctions.[18,19]

In this study, nocturia was the most common and severe symptom in all patients. Nearly all patients with MSA and PSP complained urinary symptoms. Urinary symptoms of MSA were well-known, and could be a major cause of morbidity related to lower urinary tract infections.[20,21] In gastrointestinal symptoms, constipation was most frequent in general, but patient with PSP showed that dysphagia was the most frequent and severe one. Not only the frequency, but the severity of dysphagia was most in patient with PSP, even than those of MSA. Actually, bulbar symptoms of PSP can frequently cause severe morbidity in clinical setting, such as aspiration pneumonia. The frequency of constipation was known to be similar in patients with PSP and IPD, the significance of dysphagia in PSP patients should be further addressed. In other symptoms of ADQ, almost symptoms were most common and/or severe in patient with MSA. By contribution of severity of gastrointestinal symptoms, PSP patients showed comparing severity of autonomic dysfunction with patients with MSA, with significant difference to those of IPD. These findings are compatible with other reports addressing the significance of dysautonomia of PSP, and warrant more attention of clinicians to autonomic symptoms of PSP.

The prevalence of orthostatic hypotension in parkinsonian disorders was variable according to criteria and methods. In our study, one third of patients had orthostatic hypotension and there was no difference between disease groups. Although the clinical meaning of orthostatic hypotension in the diagnosis of MSA was significant, the only difference was drop of systolic blood pressure after stand up. This could mean that orthostatic hypotension is common manifestation in parkinsonian disorders, and also that the diagnosis of MSA is not critically dependent on the presence of orthostatic hypotension.

Orthostatic hypotension was prevalent in the patient without complaint of orthostasis (40.8%). Actually, we could frequently observe elderly patients with profound orthostatic hypotension, who deny any of the traditional symptoms of orthostatic hypotension such as dizziness or light headedness. Some calls this situation as 'hypotension unawareness'. Arbogast, et al.[22] showed that the majority of patients with profound orthostatic hypotension did not show the typical symptoms (33% of total), or only atypical symptoms (24%). The unawareness of orthostatic hypotension stress the importance of blood pressure monitoring irrelevant to complaints of patients.

Scores of ADQ were not differed in patient with or without orthostatic hypotension in patients with IPD and PSP. So, orthostatic hypotension could not respect the severity or distribution of autonomic dysfunctions. But the presence of orthostatic hypotension could represent the severity of urinary and cardiovascular symptoms in MSA patients. The findings that implications of orthostatic hypotension could be different in each disorder should be further addressed.

In summary, our study found that the autonomic dysfunctions were frequent in parkinsonian disorders and the PSP and MSA patients had more severe dysautonomic symptoms than IPD patients. But the limitations of our study could be identified. First, there was no age-matched control group and the age of patients was differed between disease groups. Second, the detailed history of each dysautonomic symptoms comparing to onset of motor or other presenting symptoms were not known. Third, the effect of dopaminergic medication could not be eliminated [mean daily dopa equivalent dose; 405 vs. 177 mg (IPD vs. MSA) p=0.001]. Fourth, fluctuating symptoms according to dopaminergic medication were not addressed. Further study needed to address the impact of autonomic dysfunctions about the other non-motor symptoms and long-term prognosis.

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